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Procedia Engineering 79 (2014) 137 – 142

Procedia Engineering

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37th National Conference on Theoretical and Applied Mechanics (37th NCTAM 2013) & The 1st International Conference on Mechanics (1st ICM)

Energy of quantum dots encapsulated in biological membrane

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Abstract

Mathematical model of interaction between quantum dots and lipid bilayer is introduced. The quantum dots is encapsulated in the hydrophobic core of biological membrane and influences its bending and interstitial energy. Proposed numerical solution based on Monte Carlo simulated annealing minimizes the total energy of the system. Numerical model predicts considerably lower free energy of lipid bilayer than previous simplified analytical model. The model can be used to predict a critical size of quantum dots.

Selection and peer-review under responsibility of the National Tsing Hua University, Department of Power Mechanical Engineering

Keywords: phospholipid bilayer; bending energy; interstitial energy; quantum dot; Monte Carlo

1. Introduction

Nanotechnology involves the creation and manipulation of materials at nanoscale levels from 1 nm to 100 nm [1]. The application of nanotechnology to medicine, known as nanomedicine, concerns the use of nanomaterials to develop novel therapeutic and diagnostic modalities. Semiconductor nanocrystals, also known as quantum dots, are widely used in biological research as fluorescence imaging tools [2] and might be applied in nanomedicine as well.

Up to now, the most successful and well-developed method to prepare highly luminescent IIVI quantum dots is the TOP/TOPO synthetic approach [3]. Quantum dots prepared by this approach are hydrophobic and therefore insoluble in water. It was shown, that quantum dots might be incorporated into hydrophobic core of the biological membrane. Experimental results predicts existence of critical size of quantum dots limiting the incorporation of quantum dots in biological membrane [4].

It was shown that interaction of various substances with biological membrane might be predicted by means of mathematical modeling [5]. A model of quantum dots interaction with biological membrane has been created by assuming simplified topology of quantum dots phospholipid membrane system [6]. It was shown, that deviations from simplified shape of membrane in nonlamellar lipid phase could considerable change the free energy of the system and influence the prediction of system stability [7]. Therefore the aim of this work is to introduce new model

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Selection and peer-review under responsibility of the National Tsing Hua University, Department of Power Mechanical Engineering
doi:10.1016/j.proeng.2014.06.322

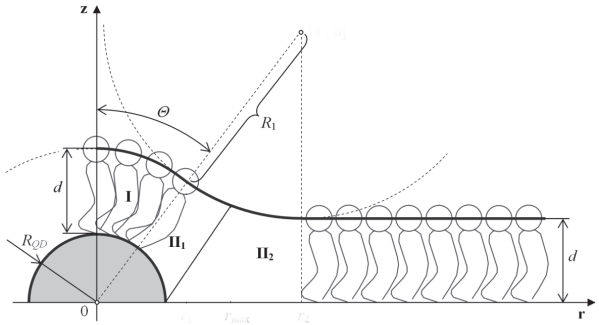

Fig. 1. Geometry of quantum dot incorporated in lipid bilayer.

of quantum dots interaction with biological membrane that will be able to account for deviations from ideal shape and compare this model to the previous simplified analytical solution.

2. Methods

The free energy of the phospholipid monolayer in nonplanar phase may be expressed in terms of bending, interstitial, hydration, and van der Waals energy contribution [7]. However, the contribution of the hydration energy in the excess water conditions is insignificant and also van der Waals energy only slightly contributes to the total free energy [8]. Thus, we consider for the total free energy of the quantum dots two energy contributions: the energy of local bending ($E_{bending}$) and the interstitial energy (voids filling energy, $E_{interstitial}$).

$$E = E_{bending} + E_{interstitial} \tag{1}$$

2.1. Bending energy of lipid monolayer

Biological membranes may be in the first approximation considered as curved and deformable smooth plates [9]. At any point at this surface, one can find a vector normal to the surface and the corresponding normal plane which contains the normal vector. There is an infinite number of such normal planes, but only two orthogonal normal planes contain curves of intersection with maximum and minimum curvature [10]. These two curvatures are named the two principal curvatures of the surface at the given point and are defined as the first and the second principal curvature, C_1 and C_2 respectively. It was shown, that the bending energy of lipid layer can be expressed as

$$E_{bending} = \frac{k_B}{2} \int_A (C_1 + C_2 - C_0)^2 \mathrm{d}A + k_G C_1 C_2 \tag{2}$$

where k_B is the bending modulus of monolayer and k_G is the Gaussian modulus or saddle splay modulus of monolayer and C_0 is intrinsic curvature of phospholipid layer. In further consideration, one can neglect Gaussian curvature term (C_1C_2) providing that the topology of monolayer is unchanged.

2.2. Interstitial energy

The need of additional interstitial energy contribution in quantum dot/phospholipid bilayer system appears due to distortion in the special packing geometry of lipids. In the lamellar phase L_α, the monolayers have a constant thickness and there are no voids in the mid-plane of the bilayer. On the other hand, inclusion of quantum dots creates a variation in distance between two adjacent monolayers. To avoid water pockets, the hydrocarbon tails of lipid molecules have

to stretch accordingly. Some of the lipid tails are stretched while other are squeezed with respect to an average length ζ_0. The void-filling energy contribution due to lipid stretching can be expressed on the basis of Hookes law [7]:

$$E_{interstitial} = \frac{\tau}{a_0} \int_A (\zeta - \zeta_0)^2 \mathrm{d}A \tag{3}$$

where ζ is the actual length of the fatty acid chain,ζ_0 is the average resting length of lipid molecule, τ is the proportionality constant reflecting the stiffness of the chains (stretching modulus), and a_0 is the average area per lipid molecule ($n = 1/a_0$ is the area density).

2.3. Geometry of quantum dots in lipid biomembrane

We assume that the inner and outer lipid monolayers are symmetrically deformed in the vicinity of the quantum dot incorporated in the lipid bilayer. Further, we assume that the lipid bilayer has a spherical shape with radius R_{QD} (Fig. 1). The problem can be described as axisymmetrical where the axis of symmetry (z-axis) is perpendicular to the bilayer plane and crosses the center of quantum dot. The first principal curvature at given point is equal to the curvature of the revolving curve describing the shape of monolayer [11].

$$C_1 = \frac{1}{R} = \frac{\mathrm{d}\vartheta}{\mathrm{d}s} \tag{4}$$

where s denotes arc length and angle ϑ is an angle that normal to the given curve makes with respect to the z-axis. Second principal curvature at given point may be computed as

$$C_2 = \frac{sin\vartheta}{r} \tag{5}$$

where r is the distance from the axis of rotation (Fig. 1).

We further assume that the average length of lipid molecule ζ_0 equals to the length of phospholipid molecule in lamellar phase L_α denoted as d in Fig. 1.

2.4. Prescribed geometry model

Wi et al, 2008 developed simplified model of quantum dots incorporation in lipid bilayer shown in Fig. 1. Within this model, it is assumed that the quantum dot induced lipid monolayer deformation profile is composed of two circular arcs with different radii. The boundary separating these two arcs is determined by the angle Θ that divides the monolayer into non-stretched and stretched region, I and II, respectively. Radius of the arc in the non-stretched monolayer (region I) is $R_{QD} + d$ which is also the radius of the two identical principal curvatures. The radius of the arc in the stretched monolayer (region II) is $R_1 = [(R_{QD} + d)\cos\theta - d]/(1 - \cos\theta)$, which is the radius of the curvature of the revolving curve. For a given radius R_{QD} and monolayer thickness d, the above elastic deformation energy (Eq. (2)) can be expressed as a function of a single parameter, angle θ.

Interstitial energy of hydroxycarbon chains occurs in region II only. Region II (Fig. 1) is divided into two local regions II_1 and II_2 where the contact occurs with the spherical quantum dots and the opposing monoloayer, respectively. The stretching energy may be expressed as a function of angle θ. Detailed derivation is provided elsewhere [6]. Angle Θ that corresponds to the minimal energy is obtained by means of differentiation,

$$\left.\frac{\mathrm{d}E}{\mathrm{d}\theta}\right|_{\theta=\Theta} = 0 \tag{6}$$

2.5. Determination of equilibrium configuration by Monte Carlo Simulated Annealing Method

In the proposed model, the configuration of monolayers adjacent to the quantum dots is described by the radius of the central cylinder and a set of N angles,ψ_i, $i = 1, 2, ..., N$ describing the surrounding monolayer, which were divided into N sufficiently small parts. The boundary conditions were introduced to reflect connections within the different parts of the system. Due to the symmetry, the first and the last angles ψ were taken as zero.

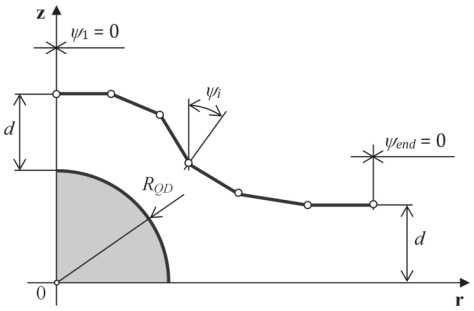

Fig. 2. Discretization of membrane momoloayer for Monte Carlo simulated annealing computation of energy.

The minimization of the free energy of the system was performed by the Monte Carlo simulated annealing sampling strategy. The method was invented by Kirkpatrick et al., 1983 as an adaptation of the Metropolis–Hastings algorithm, which constitutes the Monte Carlo method [13]. The method is inspired by physical process of annealing inmetallurgy, when the heating and subsequent slow cooling of material is used for the increase of the crystal size in the material and thus reduces defects. By analogy of this effect, each step of the simulated annealing algorithm moves the current solution to a sufficiently near random solution. The probability of excepting of a new solution depends on the difference in the corresponding function values and a global parameter T (temperature), which is decreasing during the process under a cooling schedule. For high values of temperature the randomness of the choice is considerable, thus the solution can jump out from local minima. With decreasing of temperature the probability for acceptance of a solution corresponding to higher energy is decreased, hence the solution is smoothed in a low temperature mode.

Within this approach, it is assumed that any local minimum is accessible from any other minimum after a finite number of random sampling steps [13]. In contrast to the conventional Metropolis Monte Carlo method, all values of angles ψ were updated in each step [12]. After each step, the total free energy of the system was evaluated by the Metropolis criterion [13] and compared with the free energy of the previously accepted state. To find the global minimum in the multivariational space, the simulation was started at sufficiently high temperature according to the Metropolis criterion, while according to the cooling schedule the temperature was decreased after each step until it reached the zero value. The algorithm of Monte Carlo simulated annealing was implemented in custom Java™ code.

2.6. Estimation of constants

In order to determine the free energy of different configurations of the lipid monolayers, the values of the model constants were estimated. The value of $11kT$ is the bending constant [14] and $a_0 = 0.65\ 10^{-18}$ m^2 is the area per phospholipid molecule[15]. The reference (nonstretched) length of the phospholipid tails $d = \zeta_0$ was taken to be 1.47 nm [7]. In calculation of the interstitial energy, the lipid stretching modulus τ was taken to be 0.095 kT nm^{-2} [16]. For the sake of simplicity it was taken that the molecules favor cylindrical geometry, i.e. $C_0 = 0$ [17].

3. Results and Discussion

Fig. 3 present progress of Monte Carlo simulated annealing calculation. Simulated annealing might be considered as a method of molecular dynamics describing thermal fluctuations of membrane. The lower the temperature, the lower the membrane undulations and the membrane reaches minimum energy at minimum temperature (Fig. 3d).

Analytical model was compared to the Monte Carlo simulation to verify custom written numerical procedures by prescribing simple geometry defined in section 2.4 (Fig. 4). Both models predict almost the same values of free energy when describing the same geometry. The differences between the analytical and numerical solution are below 6%. These differences may be caused by discretization of the numerical model and decreased sensitivity of numerical model at transition between the quantum dot to monolayer contact.

However, the numerical solution is able to find shapes of monolayer with considerable lower energy than simplified analytical model as shown in Fig. 5. The total energy is increased with increasing radius of the quantum dot. These

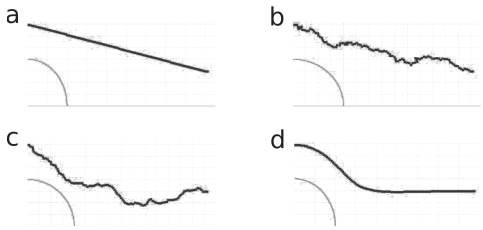

Fig. 3. Progress of Monte Carlo simulated annealing calculation. (a) starting shape, (b-d) fluctuations of the monolayer decreases with decreased parameter T.

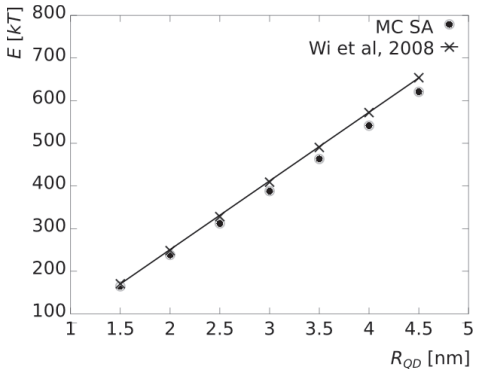

Fig. 4. Free energy of lipid bilayer with incorporated quantum dot. Comparison of analytical solution with prescribed geometry after Wi et al, 2008. and Monte Carlo solution with the same prescribed geometry, Fig. 1.

observations are in accordance with experimental measurements of Gopalakrishnan et al who observed successful incorporation of quantum dots with size 2.5 nm into liposomes [4] and he failed to observe any fluorescent emission from the lipid bilayer in the case of quantum dots with radius of 4 nm.

Wi et al, 2008 predicted that quantum dots Incorporated in the biological membrane is a more stable state than in micellar configuration for the quantum dots size smaller than a certain critical size. Wi et al, 2008 predicted this critical size to be around 3.5 nm that is consistent with experimental results. Our model shows that bilayer shape predicted by Wi et al, 2008 is not a minimum energy shape and that it is possible to find membrane topology with considerably lower energy. As the minimum energy is lower (Fig. 5), the critical size of quantum dots is likely to be increased.

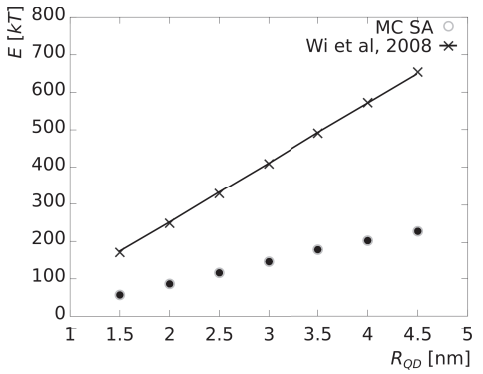

Fig. 5. Free energy of lipid bilayer with incorporated quantum dot computed using simplified analytical model and numerical model.

4. Conclusion

We suggest a theoretical model of quantum dots encapsulation in biological membrane. The model minimizes total energy of lipid bilayer in contact with quantum dots using Monte Carlo simulated annealing without any geometrical assumptions of minimum energy shape of bilayer except azimuthal symmetry. Assuming complex geometry of the bilayer incorporating quantum dots, considerably lower free energy shape can be found in comparison to simplified geometrical model.

Acknowledgments

This research was supported by Technological Agency of Czech Republic, project TA01010185.

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